DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

FEB 19 1999

The Honorable Tom Bliley, Jr.
House of Representatives
Washington, D.C. 205 15

Dear Mr. Bliley:

I am responding to your letter of January 12, 1999, in which *you* pose fifteen questions about the possible relationship of induced abortion to breast cancer, the relationship between human papillomavirus (HPV) and cervical cancer, and the National Cancer Institute's (NCI) dissemination of research findings on these topics. I regret that I could not meet your request to provide a response by January 29, 1999. My staff have worked closely with Mr. Marc Wheat to keep him informed of our progress.

As requested, the questions have been restated below. The answer fol1ows each numbered question.

1. **At the July** 20 **hearing on "The State of Cancer Research," the National Cancer Institute testimony addressed the importance of epidemiologic research in identifying the factors that increase cancer risk. How much of the NCI budget is allocated to the funding of intramural and extramural epidemiologic studies done for that purpose?**

NCI funds the bulk of this research through the Division of Cancer Epidemiology and Genetics (an estimated $60 *million for intramural epidemiologic studies)* and the Division of Cancer Control and Population Sciences (an *estimated $147 million for extramural researchers).* Additional funding from other NCI Divisions may be relevant, but we included only projects that are directly related to studying factors that increase cancer risk.

2. **NCI has a long-standing focus on "preventable causes." Are there preventable causes for breast cancer that have been identified by NCI? What preventable causes have been identified for cervical cancer?**

After discussion with Mr. Mark Wheat of your staff, "preventable" (for the purpose of this inquiry) exposures are those created by human intervention; i.e., herbicides, diet. In contrast, "unavoidable" exposures are those that occur in nature; i.e., genetics.

Breast Cancer

The leading known risk factors for breast cancer are largely unavoidable. Age is the leading risk factor, with incidence rates increasing dramatically after age 50. Family history is a strong risk factor, particularly if a woman's mother or sister has the disease. *Genetic factors* play an important role. About 50 percent of women with a mutation in the BRCA-1 gene will develop breast cancer by age 70. It is important to keep in mind that only between 5 and 10 percent of all breast cancers appear to be attributable to an inherited genetic mutation. Some *benign breast diseases* increase risk, and a *previous diagnosis of breast, ovarian* or *endometrial cancer* is associated with risk.

Reproductive events are a strong determinant of subsequent breast cancer risk. *Early menarche* and *late menopause* increase risk, while removal of both ovaries before menopause reduces risk. Having *additional births* after the first is associated with a slightly reduced risk. The most consistent reproductive factor is the *woman 's age at first full-term pregnancy.* Women without children and women having their first child after age 30 have a two- to three-fold increased risk of this disease, compared with women who give birth before age 20. A woman with an interrupted first pregnancy, either spontaneously or through induced abortion, does not reap the protective benefit of a full-term pregnancy.

Other risk factors may be considered "preventable." Taking *oral contraceptives* may increase risk for breast cancer at an early age (before age 45), and *estrogen replacement therapy* may slightly increase risk of breast cancer. Among postmenopausal women, risk increases with *weight, body mass,* and *distribution ofweight.* The association with *dietary fat* consumption is inconclusive, while recent studies have shown a fairly consistent though small effect of *alcohol* consumption on breast cancer risk. Exposure to *high doses of radiation* increases risk, although the effects of low-dose radiation are considered minimal.

Most of these "established" risk factors for breast cancer are associated with only a moderately increased risk, suggesting that multiple factors may play a role in each woman's disease, and that unrecognized factors may exist. Further research is necessary, is ongoing, and remains a high priority for the NCI.

Cervical Cancer

Sexual behavior has been identified as the major risk factor for cervical cancer. Risk is increased by *early age at first intercourse* or *numerous life-time sexual partners.* The greater the number of sexual partners, the greater the risk of *sexually transmitted disease,* which can be a risk factor. Abundant laboratory and clinical data support a role for *human papillomavirus (HPV)* in cervical cancer. *Cigarette smoking* is associated with increased risk. *Barrier methods of contraception* reduce risk, and the use of *orai contraceptives* increases risk. Giving *birth multiple times* is an independent risk factor, and vitamin C, beta carotene, or folacin (one of the B complex vitamins) *deficiencies* may increase risk.

3. **The NIH written testimony for the July 20 hearing states that "communicating with...individuals at high risk for cancer, the general public, and the health care community is a central component of NCI's mission and mandate." To that end, NCI has identified preventable target exposures of cancer-causing agents as a key element in the prevention of cancer. What work has NCI done to coordinate a Federal response to the prevention of breast and cervical cancer? Specifically, what work has NCI done with the Department of Health and Human Services Office of Population Affairs and the HHS Health Resources and Services Administration to alert women to avoidable exposure to carcinogenic agents? Who are the liaisons within NCI, HRSA, and the Office of Population Affairs? Has NCI coordinated activity with the Title V and Title XX programs within those agencies?**

Federal agencies are designated to serve the United States in specific ways. The National Institutes of Health (NIH), of which NCI is a part, is a research agency. In its mission to protect and improve human health, the NIH (and NCI) conducts and supports basic, applied, and clinical and health services research to understand the processes underlying human health and to acquire new knowledge to help prevent, diagnose, and treat human diseases and disabilities. This may include *developing an information campaign* (such as the 5 **A Day Program** described below, which was based on scientific evidence that increasing consumption of fruits and vegetables reduces cancer risk) and *evaluating its effectiveness* at achieving its goal (increasing the daily intake of fruits and vegetables). NCI also has a mandate to disseminate research findings so that when the development and evaluation are completed, other Federal and state agencies, and private sector organizations, may take this information and apply it accordingly. NCI, therefore, plays an integral role in these activities. For example, the Steering Committee for the National Action Plan on Breast Cancer (NAPBC) includes NCI staff as members and working group chairpersons serving this unique public/private trans-Federal partnership.

The NCI disseminates research findings widely through scientific publications, press conferences, press statements, clinical alerts, patient education materials, meetings of professional societies, television and radio, the World Wide Web, our toll-free Cancer Information Service, our PDQ databases, and the Information Associates Program. Our staff has many contacts within agencies for a variety of programs and issues. Through these personal contacts, and those mechanisms mentioned above, Federal agencies and offices have direct access to information pertinent to their programs. In addition, we maintain and foster close working relationships with other Institutes that have formal collaborative relationships with the Office of Population Affairs - our projects and programs are thus included in that broad knowledge base. NCI has several partnerships with other federal agencies and non-federal groups to enhance our information dissemination activities.

NCI has not formally collaborated specifically on Title V (Substance Abuse and Mental Health Services Administration) or Title XX (Adolescent Family Life Demonstration Projects) programs. As a research agency, NCI's role is to conduct and support research, then disseminate

widely new knowledge gained. Following are examples of specific information campaigns:

- **Mammography Screening -** Scientific evidence supports NCI's recommendation that lives can be saved if women in their forties or older have regular screening mammograms, every one to two years. Because this constituted a major change in the level of scientific evidence to support screening mammography, it was imperative that NCI disseminate this information widely. Specific information targeting various populations and constituencies was developed and disseminated using a variety of mechanisms, such as patient-oriented publications, education materials, public service announcements, and electronic media.
- 5 **A Day -** Because fruit and vegetable intake has been clearly demonstrated to provide a health benefit beyond cancer prevention, increasing American consumption has tremendous potential to improve our Nations health. Because health messages can be confusing, NCI set aside special funds for grantees to find innovative ways to inform the public. In an unprecedented public/private partnership, grantees and health departments nationwide participated in a study of new methods to reach the public and influence behavior. These grants are completed, and NCI and the Centers for Disease Control and Prevention (CDC) are evaluating their success. If indeed Americans increased their consumption, then other public and private groups will have scientifically proven methods to bring into their communities.
- **"Risk Disk" -** The Breast Cancer Risk Assessment Tool is a computer program that women and their health care providers can use to estimate a woman's risk of developing breast cancer for two time periods - over the next five years and for her lifetime - based on several recognized risk factors (see Question 2 for a discussion of some of those risk factors). The tool compares these risks (given as a percentage) to those of a woman of the same age with no risk factors other than her age, and with the risk of women who were eligible to participate in the breast cancer prevention trial using tamoxifen.

4. **The July 20 NCI written testimony states that "NCI is actively pursuing development of a vaccine to prevent cervical cancer...based on the concept that almost all cervical cancers are caused, at least in part, by papilloma virus infections." What is the status of the development of a vaccine for this disease? How long will it be before a vaccine enters clinical trials? Have any private sector entities partnered with NCI in the development of this vaccine?**

The vaccine is currently being developed in clinical trials. The Phase I study to determine if the vaccine can prevent infection is underway at Johns Hopkins University, and preliminary results based on laboratory tests are encouraging - with no toxicities yet reported. Following completion of the Phase I trial, a Phase II trial to determine correct dosage is expected to begin in January **2000.** A planned Phase III randomized clinical trial involving 10,000 women to test the efficacy of preventing HPV (Type 16) infection is expected to begin in about 2.5 years. As in many of our drug studies, we have partnered with a company to manufacture the virus-like particle

contained within the vaccine. The manufacturer will have no role in the evaluation of its benefit or safety.

5. **Earlier this year, the *New England Journal of Medicine* published the results of a study on human papillomavirus (HPV). Among sexually active female students at Rutgers University, approximately 60 percent tested positive for HPV at some time during the three-year study period. Given that HPV is an agent of most cervical cancer cases, which kill nearly as many women each year as AIDS, what does a 60 percent infection rate suggest to NCI about the long-term consequences of this virus? Does this infection rate suggest that condom usage is less effective at preventing HPV infection than it is in preventing pregnancy? Has NCI sponsored any research as to the effectiveness of condoms to prevent the transmission of HPV?**

Experts estimate that as many as 24 million Americans are infected with HPV, and the frequency of infection and disease appears to be increasing. For most women, HPV does not remain in the body. After initial infection, most women's immune system can clear the virus within **18** months. Therefore, a high prevalence at a point in time is not indicative of the numbers of women who will suffer health consequences. In fact, most women suffer no serious health problems as a result of HPV infection, nor do they know they have been infected. Although most HPV infections do not progress to cancer, it is important for women to have regular Pap smears. Potentially pre-cancerous cervical disease is readily treatable. By identifying women with persistent infection through screening, and then treating those with pre-cancerous conditions (by removing the pre-cancerous cervical tissue affected), we relieve most of the burden of cervical cancer from HPV infection in the United States.

Condoms are ineffective against HPV because the virus is prevalent not only in mucosal tissue (genitalia) but also on dry skin of the surrounding abdomen and groin, and it can migrate from those areas into the vagina and the cervix. Additional research efforts by NCI on the effectiveness of condoms in preventing HPV transmission are not warranted. However, condom use is extremely important for preventing the transmission of other sexually transmitted diseases, and in the prevention of pregnancy. We include the use of condoms as an option in clinical trials if methods of birth control or disease prevention are needed.

6. **What is the amount of research dollars expended on HPV as compared to the virus that causes AIDS? What is the ratio between the two research budgets as compared to the number of women who die of the respective viruses?**

There are over 80 types of HPV, about 15 of which are associated with cancer of the cervix. NCI estimates that it will spend about $38 million on cervical cancer-related HPV research, and about $235 million on AIDS-related cancers, in FY 1999.

There are about 5,000 deaths in the U.S. from cervical cancer each year, and more than 200,000 deaths world wide. Over 90 percent of these cancers are HPV-related. There were about 4,600

female deaths in the U.S., and 900,000 worldwide, from HIV-related illness in FY 1997.

7. **What action does NCI recommend be undertaken by the Federal government to address the public health threats of HPV?**

Human papillomavirus (HPV) is one of the most common causes of sexually transmitted disease in the world. The NCI believes that if all women had pelvic exams and Pap tests regularly, most pre-cancerous conditions would be detected and treated before cancer develops. At present, early detection and treatment of pre-cancerous tissue remain the most effective ways of preventing cervical cancer. This is communicated in our publications and public information. NCI is working to develop a vaccine that will prevent the main cancer-causing types of HPV, and is investigating the use of HPV testing, via more accurate Pap testing programs, to improve cervical cancer screening and prevention.

8. **According to an Associated Press report on a Supreme Court ruling dated January 11, 1999, HHS had a hand in the removal of controversial posters in the Philadelphia public transit authority that linked abortion to breast cancer. According to this report, in "Early February [1996], the authority received a copy of a letter a federal health official had sent to the Washington Metropolitan Area Transit Authority. Dr. Philip Lee, Assistant Secretary of Health in the Department of Health and Human Services, called the anti-abortion ad 'unfortunately misleading' and 'unduly alarming,' and said it 'does not accurately reflect the weight of the scientific literature.' Based on Lee's letter, SEPTA removed the posters on Feb. 16, 1996." Please provide the Committee with a copy of this letter, and copies of all other letters HHS has sent since 1993 raising concerns about ads making cancer claims that may be "unduly alarming." On what basis was the ad found to be "unfortunately misleading," "unduly alarming," and that it "does not accurately reflect the weight of the scientific literature"?**

In early 1996, NCI staff drafted a response to requests for information about the scientific evidence concerning the relationship between induced abortion and breast cancer risk. The letter was drafted for Dr. Klausner's signature **(Attachment 1)**, but there are no copies of other drafts, or of correspondence to SEPTA, signed by either Dr. Klausner or Dr. Lee in NCI's central files system or with queried staff. There were several meetings with Dr. Lee and/or members of his staff to discuss a response. We have suggested to Mr. Wheat that he ask the Department of Health and Human Services, too, to search for relevant documents. NCI did issue a press statement **(Attachment 2)** on February **14, 1996, regarding** the SEPTA campaign's representation of information from the scientific literature. A search of NCI's central files, and among files of queried NCI staff, revealed no correspondence since 1993 concerning other advertisements making other cancer claims.

9. **In a line of questioning at the July 20 hearing before the Health and Environment Subcommittee, the NCI witness was asked about a very substantial body of research**

linking cancer to what is clearly an eminently avoidable exposure which you did not mention in your written testimony. Fully 25 out of 31 epidemiologic studies worldwide and 11 out of 12 studies in the United States (many of which, I am told, were conducted or funded by the NCI) show that women who elect to have even one induced abortion show an elevated risk of subsequent breast cancer. What studies has NCI conducted or funded related to the link between abortion and breast cancer?

Note The written testimony for the July 20 hearing focused on recent advances in cancer treatment, as it was our understanding that this was the intended topic of the hearing.*

The body of research conducted before 1997 was, as described in a systematic review of the literature by respected epidemiologists, "inadequate to infer with confidence the relation between induced or spontaneous abortion and breast cancer risk, but it appears that any such relation is likely to be small or non-existent." Three points stood out in 1996. The first point was that the type of study (case-control interview studv) that dominated the scientific literature at that time was subject to a demonstrated bias ("recall bias")' that tended to create an association where such association might not actually exist. Also, many of the early studies had no controls for other important risk factors. The second point was that the published studies showed no consistency in findings - and those that did showed what epidemiologists term "a weak association" (a relative risk between **0.7** and 1.3), or difficult to distinguish from bias or chance. The third point was that it seemed unlikely that the type of study that was needed -- a study design unencumbered by recall bias, such as a cohort study -- could be performed in the United States.

Epidemiologists thus regarded with interest the very large study, reported in 1997, which examined medical records - not personal interviews - from the entire female population of Denmark. In Denmark, routinely maintained population registries of births, deaths, medical procedures, and cancer make it possible to compile the data required on a large scale *without* recall bias and with great statistical precision. The study found no increased risk of breast cancer in the Danish women who had recorded abortions, as compared with women with no record of abortion.

The NCI conducts and funds many epidemiologic studies of breast cancer. Often included in the surveys and/or questionnaires are inquiries about a woman's reproductive history which, as stated above in the response to Question 2, is a strong determinant for breast cancer. These questions typically address her history of spontaneous abortion, induced abortion, or full term pregnancy. NCI has funded three studies directly related to abortion as a possible risk factor. They are listed below:

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[1] Women under-report abortions, yet breast cancer patients are more willing to acknowledge a previous abortion than other women - a difference that produces "recall bias."

Breast Cancer in Relation to Prior Induced Abortion (completed 1990)
(PI: Daling - Fred Hutchinson Cancer Research Center, Seattle)
Induced Abortion and Risk of Breast Cancer in Shanghai (completed 1997)
(PI: Thomas - Fred Hutchinson Cancer Research Center, Seattle)
Induced Abortion and Breast Cancer Risk (expected completion 1999)
(PI: De-Kun - Kaiser Foundation Research Institute, CA)

In summary, the scientific literature does not suggest that women who have even one abortion show elevated risk. It remains true that a woman whose first pregnancy is interrupted, either by spontaneous or induced abortion, does not gain the same degree of protection against breast cancer as the woman who is pregnant for the first time at the same age and carries her first pregnancy to term; instead, she has delayed her age at first birth. The biologic effect of abortion is seen by comparing two women who give birth for the first time at the same age, one of whom had a prior terminated pregnancy. These two women have the same subsequent risk of developing breast cancer, based on the epidemiologic data available today.

10. **Research presented the Committee shows that induced abortion has been linked with increased risk of breast cancer. What has NCI done to alert women that induced abortion has been consistently associated with increased breast cancer risk? How has NCI focused its public information on at-risk populations?**

Experts at NCI and elsewhere find that the evidence suggests that induced abortion is not associated with an increased risk for breast cancer. Our information to women concerned about breast cancer risk after abortion addresses the research data to date, and includes discussions about data inconsistencies. We also emphasize the importance of a woman's discussing her personal risk of breast cancer with her physician.

In general, NCI reaches out to patients, their families, health care providers, researchers, and the public to bring them the most accurate, up-to-date cancer information. The NCI provides that information by telephone, on the Internet, through the media, in partnership with other organizations, and through a wealth of printed and audiovisual materials.

- The Cancer *Information Service* (CIS) answers about 500,000 calls a year at 19 regional offices. The toll-free number, *1-800-4-CANCER*, connects English- and Spanish-speaking callers with the office that serves their area. The CIS provides nationwide service to all 50 states and Puerto Rico. It also has an outreach program that develops partnerships with nonprofit, private, and other government agencies at national, regional, and local levels. Two-thirds of CIS partners focus on reaching minority populations.
- *PDQ* is NCI's computerized database that gives patients, health professionals, and the public quick and easy access to the latest treatment, supportive care, screening, and prevention information, as well as descriptions of clinical trials that are open for enrollment.
- NCI's *Office of Liaison Activities* works with national advocacy, voluntary, and professional organizations concerned about cancer to disseminate the latest, most

accurate cancer information, and collaborates with these groups in areas of mutual interest. These organizations influence their members, the media, the public, and policymakers.

- NCI is developing a *publication on genetic testing* to help people decide if testing is right for them. NCI is also working to increase health care professional awareness and knowledge of human genetics and related ethical, legal, and psycho-social issues.
- NCI develops *media and print materials* designed for distribution to a variety of audiences. Some of these are designed specially for minorities and the medically underserved and are often implemented as part of national campaigns. These materials support the main message of a campaign (for example, women over age 40 should have regular mammograms) but are designed to be used by community leaders. For example, some materials for mammography screening include posters in English for African-American Asian, and Native American women, and in Spanish, Vietnamese, Chinese and Korean. NCI also contributed to a nationally syndicated Spanish radio show promoting breast and cervical cancer prevention and detection.

11. **I understand that the body of worldwide epidemiological research on the link between abortion and breast cancer reaches back as far as 1957. And the first such study conducted in the United States occurred as early as 1981. Is it not a fact that a majority of these studies show an increased risk (average about 30%) among women who have chosen abortion even just once?**

The only cohort study published before 1996 found a statistically significant negative association (that is, abortion was associated with reduced risk for breast cancer). Of the 18 case-control studies published through 1996, most found no statistically significant association, positive or negative. Most of these studies did not control for known risk factors, or were limited by inadequate or possibly biased reporting of abortions. Because a very weak overall association might obscure a stronger one in a subgroup of women (perhaps young women), investigators also reported any associations noted in subgroups, even though the number of those subjects was very small. The subgroups noted to be at risk in one study were not found to be at risk in other studies. Thus, even before the large Danish cohort study was published the weight of evidence suggested no association, or a very weak one. There remains some uncertainty about the relative risk for women with very late induced abortions. More data on this finding would be valuable.

12. **The NCI website on "Abortion and Breast Cancer" states that "although it has been the subject of extensive research, there is no convincing evidence of a direct relationship between breast cancer and either induced or spontaneous abortion. Available data are inconsistent and inconclusive, with some studies indicating small elevations in risk, and others showing no risk associated with either induced or spontaneous abortions."**

A. Please identify and provide copies of the "extensive research" to which the website text refers. Was this research peer-reviewed?

I have attached copies of a systematic review of the literature published in 1996, a Dutch case-control study published later, and the large Danish cohort study **(Attachments 3, 4, and 5).** Each of these papers contain an extensive bibliography which, when taken as a whole, represent the body of literature used by NCI experts to develop the fact sheet to which you refer. All of these papers were published in peer-reviewed journals.

B. The website states that there is no "convincing evidence." What are NCI's criteria for identifying research that would be considered "convincing"? Are there statistical benchmarks that NCI uses to distinguish evidence that is convincing and that which is not? How is this evidence measured that would control for bias among researchers or program evaluators?

C. Does NCI draw a distinction between "direct relationship" and "indirect relationship" in determining causality?

D. NCI states that "available data are inconsistent and inconclusive." Are the data inconsistent, or are the studies inconsistent? What accounts for data that "are inconsistent and inconclusive"? Has NCI attempted to replicate studies that may have shown a link between breast cancer and induced abortion?

E. The NCI website states that some studies indicate a "small elevation in risk." What does "small elevation in risk" mean in this context? By saying there is a "small elevation in risk," is NCI placing the risk on a continuum between no risk and high risk? How does the "small elevation in risk" rank on a comparative risk analysis continuum? Based on this continuum, what action has NCI or other Federal agencies taken to warn consumers of cancer risk-factors that are comparable to that of induced abortion? Does "small elevation in risk" mean "acceptable risk"? How does NCI determine that something is an acceptably small risk?

Epidemiologists use the terms "weak associations" or "small risks" to express assessment of whether an association is "real"; that is, the probability that a factor causes the development of disease. Epidemiologic studies can be subject to errors of several types: biases in selection of study participants; biases in the observation of comparative data (such as the recall bias so problematic in collecting interview data on induced abortion); and statistical imprecision as the study size becomes smaller. Thus, "small" or "weak" are terms associated with the level of error methodologically expected for (1) chance occurrence, (2) a particular feature of the disease or the exposure, and (3) study design. The increased risk of developing breast cancer associated with each risk factor (see Question 2, above, for examples) varies from 1.5 to 4 times average risk.

An association typically is estimated as the ratio of risks, or the "relative risk." "Relative risk" is

the ratio of disease incidence in the exposed population to the incidence in the unexposed population. A relative risk of "1.0" means that women exposed and women unexposed to a factor have the same risk of developing disease. It is a mathematical computation well-suited for assessing biologic connection. It is not intended to address comparison of absolute risk to benefit, or to judge what is acceptable risk to each individual. The NCI publishes widely the facts known about possible breast cancer risks, but decisions about "acceptable" risks must be made by a woman and her health care provider.

For the relationship between abortion and breast cancer, the most complete current summary of the uncertainty comes from the Danish population record study. The authors estimate that the relative risk for breast cancer in women with a recorded abortion is most likely between 0.94 and 1.06, with a very narrow interval of uncertainty because the study was very large. If a relative risk of "1.0" means that women exposed and women unexposed to a factor have the same risk, then the Danish population record study demonstrates that the women exposed to - and those not exposed to - the risk factor (induced abortion) have the same risk.

In many case control studies, a relative risk of 1.3 (or equivalently, a protective effect seen in a relative risk of 0.7) would be weak, small, or low. A relative risk of 2.0 is moderate. For example, if the initial research suggestion of an overall relative risk of 1.3 for developing breast cancer after abortion were supported by large and well-controlled epidemiologic studies, and otherwise fulfilled criteria for causality (see Question 12F, below), NCI would, as with other peer-reviewed information, make that available through all our mechanisms of information dissemination (see Question 10, above). NCI takes its responsibility for the public trust very seriously. All peer-reviewed study data are considered carefully, continuously, and comprehensively before we will say with certainty that a factor imparts a cancer risk. As discussed previously, the scientific literature to date does not suggest that women who have even one abortion show elevated risk. Our publications currently reflect this.

F. NCI also states that some studies indicate "no risk." What level of "elevation of risk" is considered to be "no risk" by NCI? How is "no risk" distinguished from that of "small risk" when proving causality is so difficult?

Evaluation of causality requires consideration of various types of evidence. Whether an exposure ***causes*** cancer may be assessed via several similar schema, the most common being the Bradford Hill criteria: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence, and analogy. In many case control studies, a relative risk of 1.3 (or equivalently, a protective effect seen in a relative risk of 0.7) would be weak, small, or low. The authors of the Danish study estimate that the relative risk for breast cancer in women with a recorded abortion is most likely between 0.94 and 1.06, with a very narrow interval of uncertainty because the study was very large. This falls below the level of risk epidemiologists would consider weak, small, or low.

13. **Is it true that epidemiologic research has found no overall link between spontaneous abortion and breast cancer? Is that not also consistent with the fact that most pregnancies which abort spontaneously are characterized by subnormal estrogen levels, whereas normal pregnancy levels of estrogen are several times higher than non-pregnant levels? Is it also true that some form of overexposure to estrogen, which stimulates the growth of both normal and pre-cancerous breast tissue, is the mechanism by which most of the known breast cancer risk factors operate?**

Yes, it is true that research has found no overall link between spontaneous abortion and breast cancer. There are many causes of spontaneous abortion, and not all of them are characterized by subnormal estrogen levels. Breast cancer is a cancer that is hormonally responsive, but it is unclear that estrogen is the only hormone involved. Other hormones may also play an important etiologic role.

14. **The NCI website's first paragraph concludes with the sentence: "The scientific rationale for an association between abortion and breast cancer is based on limited experimental data in rats, and is not consistent with human data." Is this data to which you refer the Russo and Russo 1980 study? Is it accurate to summarize that this study, where rats were all given a chemical carcinogen, most of those rats which were allowed to bear offspring *did not* get breast cancer, while most of those which had their pregnancies surgically aborted *did* get breast cancer?**

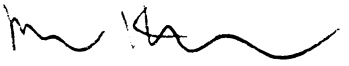
The data referred to in the NCI Fact Sheet on the Web site is the Russo & Russo study data. For breast cancer studies, suitable animal models have not been found, so extrapolating from animal data to the human model may not infer an absolute comparison. Russo & Russo found that pregnant rats who carried to term developed fewer mammary tumors than did rats who never were pregnant, or whose pregnancies were terminated.

15. **The NCI website refers to studies finding "small elevations in risk" in the link between abortion and breast cancer. A 1994 Howard University study on African-American women here in the Washington, DC area showed a more than three-fold increase in breast cancer risk with induced abortion. That same study showed that the risk was almost five-fold for African-American women over 50 years old. Is it accurate to call that kind of risk elevation "small"?**

Abortion was not a risk factor studied in the project referred to above. The risk you cite was actually the risk associated with a family history of breast cancer among women with two or more abortions. This was not the risk associated with abortion.

Please do not hesitate to contact me if you have further questions.

Sincerely,



Richard D. Klausner
Director

Attachments